Journal of the American College of Cardiology Vol. 48, No. 4, 2006

Published by Elsevier Inc.
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.05.031

EDITORIAL COMMENT

Desperately Seeking a Randomized Clinical Trial of Resynchronization Therapy for Patients With Heart Failure and Atrial Fibrillation*

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The twin epidemics of modern cardiovascular disease, atrial fibrillation (AF) and heart failure (HF), present terribly important management challenges. When these 2 conditions co-exist, an effective strategy to ameliorate symptoms, limit hospitalization, and improve prognosis is a critical objective given their prevalence and clinical and economic consequences (1,2). Although much recent, even remarkable, progress has been made, there remain major clinical subgroups in which the application of new therapeutic tools is still poorly defined.

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In the HF patient, the likelihood of co-existent AF is strongly related to the underlying New York Heart Association (NYHA) functional class. In approximate terms, the prevalence of AF is 5% for NYHA functional class I, 10% to 25% for class II to III, and as high as 50% for class IV (3). In addition, for the HF patient in sinus rhythm, the annual incidence of AF is approximately 5%. The development of AF is difficult to predict (4), but risk is greatest in those with atrial conduction delay (5) or evidence of atrial mechanical dysfunction (4), suggesting that an atrial myopathy accompanies the HF condition and paves the way for the electrophysiologic abnormalities that promote AF (6). Indeed, pathologic damage, including fibrosis, to the atria becomes evident more quickly and more extensively than the ventricles in tachycardia models of HF (7,8) suggesting that the atrial myopathy of HF is an early and consistent component of the HF condition. The development of AF in the HF patient often heralds a worse prognosis (9,10). For example, in the Framingham study, the risk of death approximately doubled in HF patients who experienced AF (9).

Atrial fibrillation is generally associated with a nonphysiologic rapid ventricular rate, which in and of itself may create cardiomyopathy or aggravate underlying ventricular dysfunction. Rate control thus becomes critically important, and medical therapy with beta-receptor antagonists is usually employed. Additional measures include digoxin and sometimes amiodarone. Some patients may benefit from atrioventricular (AV) junctional ablation to permanently eliminate tachycardia by deliberately creating complete heart block; rate is then controlled, and rhythm is regularized via an implanted permanent pacemaker. This technique is commonly known as "ablate and pace." For patients with refractory tachycardia despite medical therapy, or when medications are poorly tolerated, this approach can improve quality of life and ventricular function (11,12). Generally, this invasive strategy has been reserved for the small numbers of patients who meet stringent criteria because it renders the patient pacemaker-dependent.

Cardiac resynchronization therapy (CRT) has recently been introduced to correct ventricular dyssynchrony present in many patients with bundle branch block and HF. Substantial laboratory and clinical experience preceded small- and large-scale clinical trials, and ultimately brought this innovative technology to the clinic with established indications, namely NYHA functional class III to IV, left ventricular ejection fraction (LVEF) $<35\%$, and QRS duration >120 to 130 ms. Interestingly, virtually all patients who participated in the clinical investigations of CRT were in sinus rhythm, and there is precious little experience of applying CRT in patients with HF and AF.

Why does it matter if the patient who may otherwise qualify for CRT has AF? Patients with AF have no AV synchrony, so coordinated AV pacing with appropriately programmed AV intervals is not possible. Thus, biventricular pacing delivery, and more importantly capture, cannot be reliably assured. Patients with AF often have consistent or intermittent excessive ventricular rates, necessitating pacing at higher than desired programmed pacing rates, if indeed pacing can keep up with the underlying rate and pattern. Special pacing features can attempt to consistently overtake the spontaneous rhythm, but may do so at the expense of higher rates or may not be consistently effective. Even when pacing is delivered, many ventricular complexes may be fused or pseudo-fused, making pacing capture percentages retrievable from the CRT device inaccurate and an overestimate of effective pacing capture. It is generally believed that near maximal effective and complete biventricular capture is necessary to assure optimal CRT response.

Although CRT has now undergone rigorous and thorough investigation, only 1 randomized clinical trial permitted enrollment of patients with AF, and all others were restricted to patients in sinus rhythm. This trial, MUSTIC (Multisite Simulation in Cardiomyopathies), was a randomized crossover 6-month investigation; a substudy (13) enrolled patients with NYHA functional class III heart failure,

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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ejection fraction <35%, left ventricular end-diastolic diameter >60 mm on echocardiogram, a right-ventricular-paced QRS duration >200 ms, persistent AF of at least 3 months duration, and "a slow ventricular rate, either spontaneously or induced by AV node radiofrequency ablation." This latter entry criterion is important to emphasize because it distinguished a subset of patients with AF and HF who were much more likely to have a high degree of effective ventricular capture. The study enrolled 64 patients, but ultimately only 39 completed both crossover phases, greatly hampering the study's impact. The intent-to-treat analysis found no significant difference in the primary end point, the 6-min walk test. Although this trial described some positive trends in secondary end points and analyses, and other acute hemodynamic studies (14) or nonrandomized observational reports (15,16) suggested benefit, the reality is that it is still unclear if and to what degree CRT provides long-term benefit to patients with AF and HF, and how to reliably achieve the necessary rate control for CRT to be effective in the setting of AF.

The paper by Gasparini et al. (17) published in this issue of the *Journal* brings fresh and intriguing data to this void. This unique report describes the outcome of over 600 prospectively followed patients treated with CRT at 2 European centers. Of the 114 patients with AF, a shockingly low proportion, 42%, achieved "adequate" biventricular capture (arbitrarily defined as >85% at 2 months) despite the usual pharmacologic and pacing programming efforts. Those who did not achieve adequate capture, by protocol design in a nonrandomized format, underwent AV junctional ablation resulting in near complete biventricular capture. Reassuringly, patients with AF and patients with sinus rhythm had similar benefits from CRT across multiple relevant end points. But it is within the AF group that the results yielded compelling and provocative data. Only the patients with AF who had undergone AV junctional ablation demonstrated evidence of reverse remodeling (increased LVEF, decreased left ventricular end-systolic volume) and functional improvement. A substantial overall response rate (about two-thirds) was seen in the ablated patients, but a very poor response rate (<20%) was observed in the nonablated patients. The authors attributed this beneficial response to the imposition of AV junctional ablation after CRT, resulting in predictable and consistent 100% ventricular capture versus the capture rate of 88% in the group that did not undergo ablation.

Certainly this study's outcomes and explanations are plausible and logical. The ablation renders the patient pacemaker-dependent thus ensuring that CRT is perfectly, fully, and consistently invoked without fusion or pseudofusion; inadequate rate control is removed from even an intermittent event, and the rhythm is regularized, imparting that additional benefit on ventricular performance (18). The results suggest that even relatively high percentage biventricular capture may be inadequate, which has the practical message that all CRT patients should be regularly interrogated to ensure close to 100% capture and, if not, to take prudent measures to achieve this goal regardless of underlying rhythm.

This is an important large observational study, but the results must be interpreted cautiously. The study did not randomly allocate the ablation therapy, and it is possible that the nonablated group differed in some important way that affected outcome. On the surface, there were no important differences between the groups, but unmeasured variables certainly may have been discrepant. The relative contributions of better rate control and CRT in the ablated group could not be discerned. It is also conceivable that the perceived need to perform ablation was triggered by factor(s) that simply identified a group of patients who were destined to respond to CRT regardless of the imposition of ablation. Although unlikely, continuation of drugs in the nonablated group to achieve rate control, which were not needed in the ablated group, may have unexpectedly influenced some end points (19). The interrogation of ventricular pacing percentage was performed only once and may have been inaccurate or unrepresentative. No data are available regarding hospitalization and mortality. The foregoing discussion is most relevant to those with permanent AF; patients with paroxysmal AF or AF of shorter duration may have a rhythm control approach with appropriate drug or ablation strategies. However, concern over long-term risk (19) of chronic antiarrhythmic drug therapy will likely temper enthusiasm for this approach.

After this excellent report, it is time to define the most effective device system and intervention for patients with advanced HF and permanent AF. This study suggests that simply inserting a CRT device will not be effective in many of these patients, perhaps the majority—this is a major concern. The results of this study also beg the question of whether *all* patients with advanced refractory HF and permanent AF should have AV ablation before CRT. Certainly, recent data (20–22) have laid the groundwork for more frequent use of the "ablate and pace" approach in some specific clinical contexts, but to create pacemaker dependency in large numbers of HF patients will require definitive results from a well-designed and powered randomized clinical trial.

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